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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,658	04/07/2005	Maria Foti	100506-00025	9098

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EXAMINER
LEE, JAE W

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
02/22/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/530,658	FOTI ET AL.	
	Examiner	Art Unit	
	JAE W. LEE	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/29/2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 April 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/07/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application status

The preliminary amendment, filed on 04/07/2005 is acknowledged, wherein Applicants have amended claims 10-14 and 16-21.

Claims 1-24 are pending in this application.

Priority

A claim of priority to applications, PCT/EP03/11626, filed on 10/21/2003, and EUROPEAN PATENT OFFICE (EPO) 02023452.2, filed on 10/21/2002, is acknowledged.

Election

Applicant's species election of position 55 and SEQ ID NO: 4 with traverse in the reply filed on 11/29/2007, is acknowledged.

Applicants' traversal is on the basis that the claimed photoproteins, which may have amino acid substitutions at different positions and different SEQ ID Nos., do not have different effects. Applicants submit that all of the mutations encompassed by the claimed photoprotein are located in the region comprised between the first two calcium binding sites, which were found by Applicants to be involved in bioluminescence regulation (see specification, page 4, lines 1-3). As such, Applicants submit that the claimed photoproteins are "so linked as to form a general inventive concept" (PCT Rule

13.1). Further, Applicants submit that the restriction/election of species requirement is improper, because according to the Manual of Patent Examining Procedure, "the Commissioner... will permit a reasonable number of such nucleotide sequences to be claimed in a single application" (MPEP § 2434).

Applicants' argument is found persuasive to overcome previous restriction/election requirement with respect to SEQ ID NOs: 4 and 5 because there is ~98% sequence homology between SEQ ID NOs: 4 and 5.

With respect to various substitution positions, Applicants' assertion, that all the substitution positions have the same effect, is found to be unsubstantiated because substituting at such position(s) with hydrophobic amino acids, such as phenylalanine, can have a drastic difference in the proteins' biological function when compared to one that was substituted with a positively charged amino acids such as lysines or arginines. Such mutations can also affect antibody recognition at those positions. Taken together, each substitution has different effects. Therefore, the species election requirement is deemed proper.

Drawings

The drawings are objected to because they lack Figure 3, which the specification refers to on pg. 8-9.

Appropriate correction is required.

Claim Objections

Claims 8 and 18 are objected to because of the following informalities:

Claims recite "SEQ ID N." or “SEQ. N.” which can be improved with respect to form. The Examiner suggests replacing the noted phrases with ---SEQ ID NO:---.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-24 recite the phrase, “a region of Obelin protein comprised between the first and the second calcium binding sites,” which is unclear and indefinite. It is unclear with respect to where this "region" is. According to specification on pg. 4, Applicants disclose that the replaced region of Obelin can be between amino acid residues 42-122. However, such statement and the relevant references in the prior art do not define what “the first and the second calcium binding sites” are. For instance, where are the first and the second calcium binding sites? Are they anywhere in the amino acid sequence 1-41

and 123-195 of Obelin, respectively? Or are they in the amino acid sequence 30-41 and 123-134 of Obelin, respectively? Or are the binding sites comprise specific amino acid residues with in the amino acid sequence 30-41 and 123-134 of Obelin?

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-24 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are directed to genera of (1) chimeric photoproteins obtained by replacing any region of Obelin protein comprised between the first and the second calcium binding sites with any corresponding region of a photoprotein selected from Clytin, Aequorin, Thalassicolin, Mitocromin, Mnemiopsin and Berovin; (2) any fusion protein containing the photoprotein of claim 1; (3) any conjugation product between a photoprotein according to claim 1 and a molecule for analytical, diagnostic or therapeutic use; (4) any isolated nucleic acid molecule encoding a chimeric photoprotein according to claim 1; (5) the use of a chimeric photoprotein according to

claim 1, in combination with a luciferin substrate, for the detection of calcium ions; (6) a host cell bearing any nucleic acid molecule according to claim 12; (7) a method for producing a photoprotein, which comprises growing the host cell of claim 18 in conditions suitable for photoprotein expression, and recovering the expressed protein; (8) a method for the screening of biologically active molecules, which comprises exposing a cellular host according to claim 18 to a definite amount of said molecules and detecting any variation of intracellular calcium concentration; (9) the use of a conjugation product according to claim 11 in a competitive solid-phase immunoassay for determining the amount of said molecule in biological samples; and (10) a bioluminescence resonance energy transfer (BRET) system, comprising a fluorescent protein and any photoprotein of claim 8.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of [compositions or methods], it must be clear that: (1) the identifying characteristics of the claimed [compositions or methods] have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed.

The specification discloses only a single representative species of a chimeric photoprotein comprising the amino acid sequence as set forth in SEQ ID NO: 3, encoded by the nucleic acid sequence as set forth in SEQ ID NO: 4. However, this single disclosed species fails to provide adequate written description for the recited

genus of chimeric photoproteins, which encompasses chimeric photoproteins obtained by replacing any region of Obelin protein comprised between the first and the second calcium binding sites with any corresponding region of a photoprotein selected from Clytin, Aequorin, Thalassicolin, Mitocromin, Mnemiopsin and Berovin, optionally having any amino acid sequence attached to N- and/or C-terminal of the first and the second calcium binding sites.

In this case, the specification fails to describe any identification of structural characteristics or properties of a genus of chimeric photoproteins obtained by replacing (1) any region of Obelin protein comprised between the first and the second calcium binding sites with (2) any corresponding region of a photoprotein selected from Clytin, Aequorin, Thalassicolin, Mitocromin, Mnemiopsin and Berovin, (3) optionally having any amino acid sequence attached to N- and/or C-terminal of the first and the second calcium binding sites. Furthermore, the specification fails to adequately describe the genera of chimeric photoproteins that can be obtained using combinations of aforementioned structures in (1)-(3), so that such proteins retain the relevant biological functions, i.e., the ability to trigger enhanced luminescence upon binding calcium compared to the wild-type Obelin. For instance, the specification fails to describe a genus of chimeric photoproteins obtained by replacing (1) as little as 1 amino acid residue to as much as all of Obelin protein anywhere between the first and the second calcium binding sites, with (2) a corresponding region of a photoprotein selected from Clytin, Aequorin, Thalassicolin, Mitocromin, Mnemiopsin and Berovin, which can be any amino acid sequence/fragment comprising 1 or more amino acid residues from a

photoprotein selected from Clytin, Aequorin, Thalassicolin, Mitocromin, Mnemiopsin and Berovin, (3) optionally having any amino acid sequence attached to N- and/or C-terminal of the first and the second calcium binding sites. Such broad genus of chimeric proteins having the ability to trigger enhanced bioluminescence upon binding calcium compared to the wild-type Obelin, as the Applicants intended (see pgs. 3-4 of the specification). Taken together, the genera of "chimeric photoproteins," nucleic acid sequences encoding said chimeric photoproteins, and related methods of making and using said chimeric photoproteins encompasses widely variant species, having essentially any structure and function. Please refer to the M.P.E.P. section 2163 [R-5] under II, A, 3, (a), (ii) for more details with respect to sufficient number of representative species that should be disclosed to describe a widely variant genus.

Given the lack of additional representative species of the genera of "chimeric photoproteins," nucleic acid sequences encoding said chimeric photoproteins, and related methods of making and using said chimeric photoproteins encompasses widely variant species, having widely variant structures, as encompassed by the claim, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, because the specification, while being enabling for a chimeric photoprotein comprising the amino acid sequence as set forth in SEQ ID NO: 3, encoded by the nucleic acid sequence as set forth in SEQ ID NO: 4, does not reasonably provide enablement for (1) any chimeric photoprotein obtained by replacing any region of Obelin protein comprised between the first and the second calcium binding sites with any corresponding region of a photoprotein selected from Clytin, Aequorin, Thalassicolin, Mitocromin, Mnemiopsin and Berovin; (2) any fusion protein containing the photoprotein of claim 1; (3) any conjugation product between a photoprotein according to claim 1 and a molecule for analytical, diagnostic or therapeutic use; (4) any isolated nucleic acid molecule encoding a chimeric photoprotein according to claim 1; (5) the use of a chimeric photoprotein according to claim 1, in combination with a luciferin substrate, for the detection of calcium ions; (6) a host cell bearing any nucleic acid molecule according to claim 12; (7) a method for producing a photoprotein, which comprises growing the host cell of claim 18 in conditions suitable for photoprotein expression, and recovering the expressed protein; (8) a method for the screening of biologically active molecules, which comprises exposing a cellular host according to claim 18 to a definite amount of said molecules and detecting any variation of intracellular calcium concentration; (9) the use of a conjugation product according to claim 11 in a competitive solid-phase immunoassay for determining the amount of said molecule in biological samples; and (10) a bioluminescence resonance energy transfer (BRET) system, comprising a fluorescent

protein and any photoprotein of claim 8. as encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

Claims 1-24 are so broad as to encompass any chimeric photoproteins obtained by replacing any region of Obelin protein comprised between the first and the second

calcium binding sites with any corresponding region of a photoprotein selected from Clytin, Aequorin, Thalassicolin, Mitocromin, Mnemiopsin and Berovin, optionally having any amino acid sequence attached to N- and/or C-terminal of the first and the second calcium binding sites.

However, the specification discloses a single example of a chimeric photoprotein comprising the amino acid sequence as set forth in SEQ ID NO: 3, encoded by the nucleic acid sequence as set forth in SEQ ID NO: 4._With regard to the use of all "chimeric photoproteins" obtained by replacing any region of Obelin protein comprised between the first and the second calcium binding sites with any corresponding region of a photoprotein selected from Clytin, Aequorin, Thalassicolin, Mitocromin, Mnemiopsin and Berovin, optionally having any amino acid sequence attached to N- and/or C-terminal of the first and the second calcium binding sites as encompassed by the claims, it is noted by the Examiner that not all structurally different "chimeric photoproteins" would be able to undergo enhanced bioluminescence compared to bioluminescence of the wild-type Obelin protein. For this reason, any chimeric photoprotein obtained by replacing any region of Obelin protein comprised between the first and the second calcium binding sites with any corresponding region of a photoprotein selected from Clytin, Aequorin, Thalassicolin, Mitocromin, Mnemiopsin and Berovin, optionally having any amino acid sequence attached to N- and/or C-terminal of the first and the second calcium binding sites would not work if the critical amino acid residues contribute to the proper function of enhanced bioluminescence or calcium binding were mutated. For instance, if the entire region between the first and the

second calcium binding sites of Obelin was replaced with any corresponding amino acid sequence, i.e., 2 amino acid residues from Clytin, Aequorin, Thalassicolin, Mitocromin, Mnemiopsin and Berovin, further comprising any amino acid sequence attached to N- and/or C-terminal of the first and the second calcium binding sites, some of which can be of integral importance with respect to attaining the desired biological function, i.e., enhanced bioluminescence upon calcium binding, such “chimeric photoproteins” would not enable one of skill in the art to practice methods of detecting calcium binding via enhanced bioluminescence compared to the wild-type Obelin photoprotein. Therefore, the disclosure of a chimeric photoprotein comprising the amino acid sequence as set forth in SEQ ID NO: 3, encoded by the nucleic acid sequence as set forth in SEQ ID NO: 4 does not commensurate with the breadth of claimed products encompassing the use of all possible chimeric photoproteins obtained by replacing any region of Obelin protein comprised between the first and the second calcium binding sites with any corresponding region of a photoprotein selected from Clytin, Aequorin, Thalassicolin, Mitocromin, Mnemiopsin and Berovin, optionally having any amino acid sequence attached to N- and/or C-terminal of the first and the second calcium binding sites.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to

modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any chimeric photoprotein obtained by replacing any region of Obelin protein comprised between the first and the second calcium binding sites with any corresponding region of a photoprotein selected from Clytin, Aequorin, Thalassicolin, Mitocromin, Mnemiopsin and Berovin, optionally having any amino acid sequence attached to N- and/or C-terminal of the first and the second calcium binding sites, any nucleic acid sequence encoding said chimeric photoproteins, and any methods of making and using said chimeric photoproteins because the specification does not establish: (A) regions of any chimeric photoprotein which may be modified without affecting the enhanced bioluminescence upon calcium binding; (B) the general tolerance of any chimeric photoprotein to modification and extent of such tolerance without affecting the enhanced bioluminescence upon calcium binding; (C) adequate guidance with respect to the structure of any “corresponding region" of Clytin, Aequorin, Thalassicolin, Mitocromin, Mnemiopsin and Berovin, which can be inserted at any location between the first and the second calcium binding sites without affecting the enhanced bioluminescence upon calcium binding; (D) a rational and predictable scheme for modifying any chimeric photoprotein with an expectation of obtaining the desired activity/utility, i.e. enhanced bioluminescence and calcium binding; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Because of this lack of guidance, and the fact that the relationship between the polypeptide sequence of a protein and its activity/function is not well understood and unpredictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to make and use the claimed inventions.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any chimeric photoprotein having the desired biological characteristics, any nucleic acid sequence encoding said chimeric photoprotein, and any methods of making and using said chimeric photoprotein, is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

Claims 1-24 are rejected for the reasons as stated above. Applicants must respond to the objections/rejections in this Office action to be fully responsive in prosecution.

The instant Office action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jae W Lee, Ph.D./
Examiner, Art Unit 1656

/Richard G Hutson, Ph.D./

Primary Examiner, Art Unit 1652

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